PHARMALEX
CONFIDENCE BEYOND COMPLIANCE

Analytical similarity and comparability: what is the question ?

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With acknowledgements to:

EFSPI Working Group on Statistical methodology for comparative assessment of quality attributes in drug development:

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Process or Product (I) ?

When dealing with CMC and **Quality Attributes:**

- Is the central question about comparing processes or comparing products ?
- Patients receive individual batches
- Individual batches will be released to patients in the future
- The lots are the experimental units and central to the question
  - By contrast, in a clinical trial the patients are the experimental units used to estimate the efficacy/safety of a product.

Process or Product (II) ?

When dealing with CMC and **Quality Attributes:**

- Should the “acceptance limits” apply
  - to the Process and **individual** units ?
  - to the Product and the **means** and/or the **variances**?
- How to justify clinically defendable limits for mean or variance of process?
- Should the decision be made on current (past) batches or on future “capability” to produce lots within “acceptance limits” given observations.
- The range of the batches is important for the patient safety and efficacy.

Specifications and acceptance limits

- In pre/post manufacturing change
  - the specifications are known and constant values.
- For biosimilars
  - specifications are (by definition) unknown
  - should be established and justified and therefore are random variables.
- Specifications ~ Acceptance limits
  - specifications are about individual batches.
  - Why should it be different for biosimilars ?
  - ➔ Acceptance limits for biosimilar should be defined with the same idea.

Clinical data available

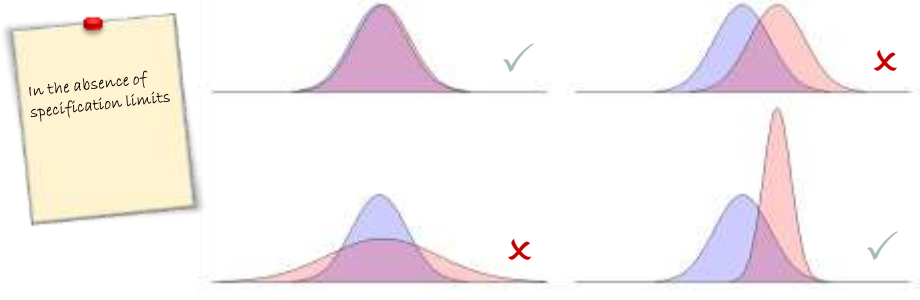
- If a “reference” product is on the market
  - it is within specifications
  - It is clinically acceptable
- The range of values obtained for “reference” batches
  - Are by definition clinically acceptable values and justified
  - Applies to the individual batches and are natural “acceptance limits”
  - How to figure out the real range of values patients are exposed to ?
- How can “acceptance limits” be built for the mean or variance based on range of individual batches?
- How can “acceptance limits” be built for the process if the mean and the variance are estimated with uncertainties
  - ➔ Bayesian statistics

Three fundamental proposals

- **Objective:** Define what is a Biosimilar or Comparable drug product
- **Decision**: Provide a well-defined decision procedure for the objective
- **Properties**: Demonstrate the operating characteristics of the procedure
  - What is the probability of deciding in favour of similarity/comparability, ie the objective?
  - What is the patient risk?
    - Test product is deemed similar/comparable and a patient receives a bad lot from the Test product
  - What is the producer risk?
    - Test product is deemed not to be similar/comparable when it is

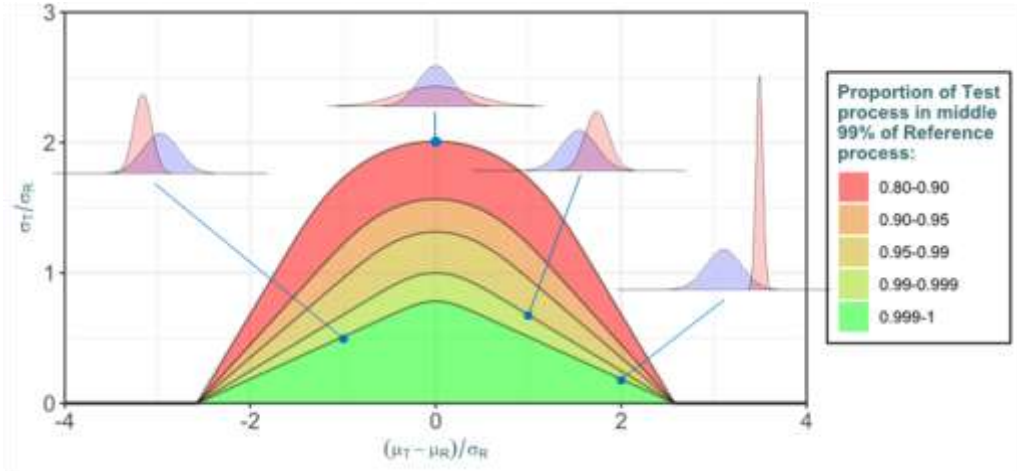
A Definition of Biosimilarity

- The test product is analytically comparable (for a given attribute) to the reference product if the middle P% of all lots produced by the Test product process lie within the middle P% of the lots produced by the Reference product process.
- In what follows we will use 99%.



A Definition of Biosimilarity

- Combinations of Mean and SD that would be considered Biosimilar



1- Define Acceptance limits (Biosimilars, otherwise use Specifications)

- Interested in limits defined by central portion of distribution of Reference product lots
- Mean and variance of Reference estimated with uncertainty
- The β-content γ-Confidence Tolerance Interval (TI) on Reference is proposed

$$[L_r, U_r] = \bar{X}_{Ref} \pm k_c \times s_{Ref}$$

Where $k_c : P_{\bar{X}_{Ref},\, s_{Ref}} \left\{ P_X \left(\bar{X}_{Ref} - k_c s_{Ref} < X < \bar{X}_{Ref} + k_c s_{Ref} \,\middle|\, \bar{X}_{Ref}, s_{Ref} \right) > \beta \right\} = \gamma$

- Takes into account the uncertainty on the Mean and the Variance
- Better statistical properties than Min and Max
- A minimum sample size of Reference is recommended to make β-content γ-Confidence Tolerance Interval (TI) relevant for Similarity limits. (Here we will use 10)

A test for Biosimilarity: 2- Future capability of Test process

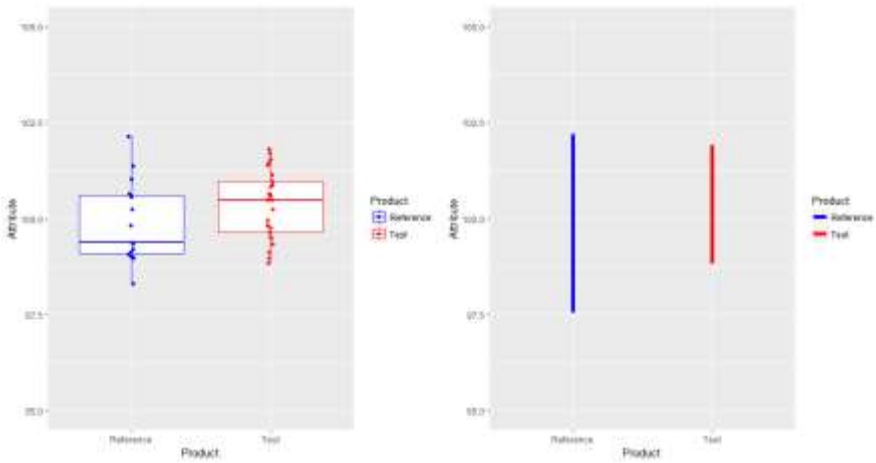
- Test if β-Prediction Interval (PI) of biosimilar is within β-γ-Tolerance Interval (TI) of reference

$$\overline{X}_{Test} \pm t_{(1+\beta)/2,(n_{Test}-1)} \times s_{Test} \sqrt{1+1/n_{Test}}$$

- More relevant than using an arbitrary c factor (such as 3!)
- Takes into account the variability of the Test process (between-lots)
- Takes into account uncertainty on means and variability of new process
- Demonstrates that Test lots will be within the range of Reference lots with some level of confidence even in the future
- Equivalent to a 100β% Credible Interval based on Posterior Predictive Distribution of X given the observed data using a Jeffreys Prior

Graphically

- Test if β-Prediction Interval is within β-γ-Tolerance Interval



A Quality approach: 2- Will Test process be capable ?

- Compute Predictive Probability (PPT) of biosimilar is within acceptance limits $[L_r, U_r]$
- Suppose we have a reference process
  - $X_t \sim N(\mu_t, \sigma_t^2)$
  - $x_t = (x_{t1}, \ldots, x_{tn})$ is a sample from test drug product.
- The posterior predictive distribution is given by:

$$p(\tilde{x}_t|\boldsymbol{x_t}) = \iint p(\tilde{x}_t|\mu_t, \sigma_t^2)\, p(\mu_t, \sigma_t^2|\boldsymbol{x_t}) d\mu_t d\sigma_t^2$$

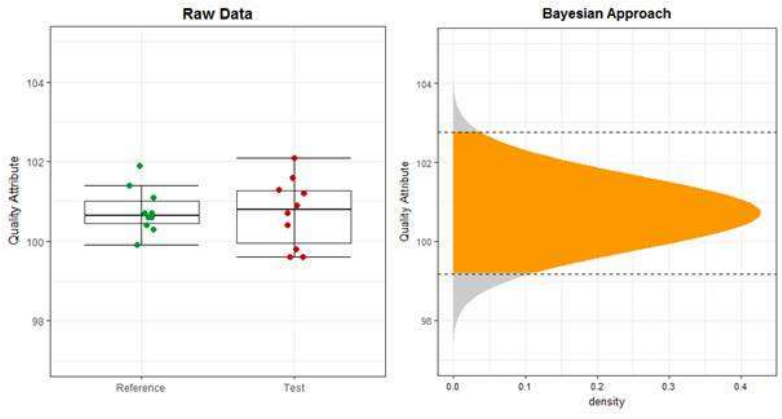
- The biosimilarity assessment proceeds by integrating the predictive over the acceptance limits

$$Pr(Biosimilarity|Data) = \int_{L_r}^{U_r} p(\tilde{x_t}|\boldsymbol{x_t})$$

$$= \Pr(L_r \leq t_{n-1}[\bar{x}, s^2(1+\tfrac{1}{n})] \leq U_r).$$

- Biosimilarity is concluded if $Pr(Biosimilarity|Data) \geq \pi$, the required **quality level**, usually 0.9.

A Decision Procedure for Biosimilarity (3)



A Definition of (Analytical) Biosimilarity

- For normally distributed processes $N\left(\mu_T, \sigma_T^2\right), N\left(\mu_R, \sigma_R^2\right)$ comparability region only depends on difference in means and standard deviation relative to the Reference standard deviation:

$$\mu_\Delta = \frac{\mu_T - \mu_R}{\sigma_R}; \rho = \frac{\sigma_T}{\sigma_R}$$

$$\left\{(\mu_\Delta, \rho) : \Phi\left[\frac{z_{(1+P_R)/2} - \mu_\Delta}{\rho}\right] - \Phi\left[\frac{-z_{(1+P_R)/2} - \mu_\Delta}{\rho}\right] \geq P_T\right\}$$

From Mike Denham, GSK

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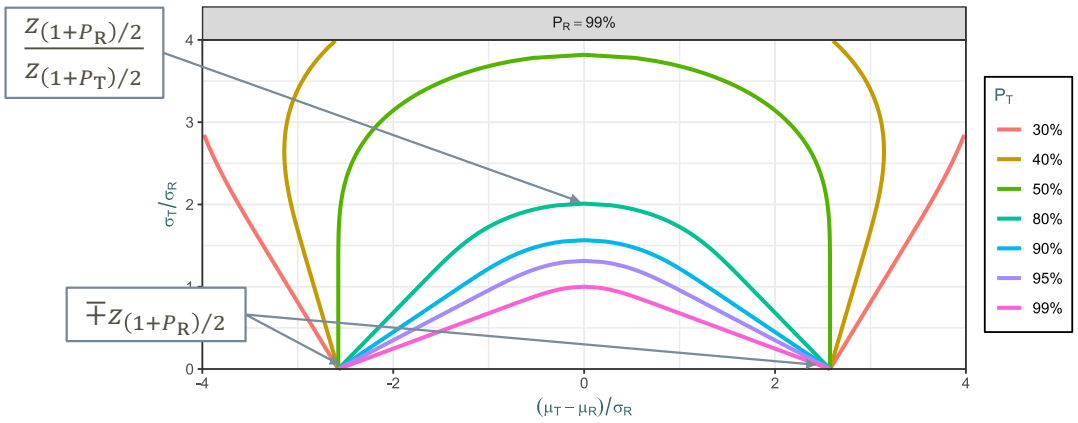
Comparability regions for P_R = 99%



From Mike Denham, GSK

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Posterior Probability of Biosimilarity

- In principle, calculating the posterior probability of Biosimilarity is easy:
  1) Define an indicator function for Biosimilarity in terms of the unknown parameters:

$$B(\mu_\Delta, \rho) = \begin{cases} 1 & \Phi\left(\frac{z_{(1+P_R)/2} - \mu_\Delta}{\rho}\right) - \Phi\left(\frac{-z_{(1+P_R)/2} - \mu_\Delta}{\rho}\right) \geq P_T \\ 0 & \text{otherwise} \end{cases}$$

  2) "Integrate" this over the unknown parameters weighted by the joint posterior density:

$$P(\text{Biosimilarity}|\text{Data}) = \int_{\sigma_R, \sigma_T, \mu_T, \mu_R} B\left(\frac{\mu_T - \mu_R}{\sigma_R}, \frac{\sigma_T}{\sigma_R}\right) P\left(\mu_T, \mu_R, \sigma_T, \sigma_R|\text{Data}\right)$$

From Mike Denham, GSK

Comparison with other approaches – original FDA Tier Approach

Tier 1 – Equivalence
(1-2α)100% two-sided Confidence Interval for Difference in Means contained within +/-1.5s_{Ref}

Compares the means of the two distributions
No more in new FDA Guidance

Tier 2 – Range
Quality Range Method: mean +/- k s_{Ref}

Compares the central portions of the two distributions

Tier 3 – Least Critical
Raw Data/Graphical Comparison

No 'formal' assessment of the two distributions

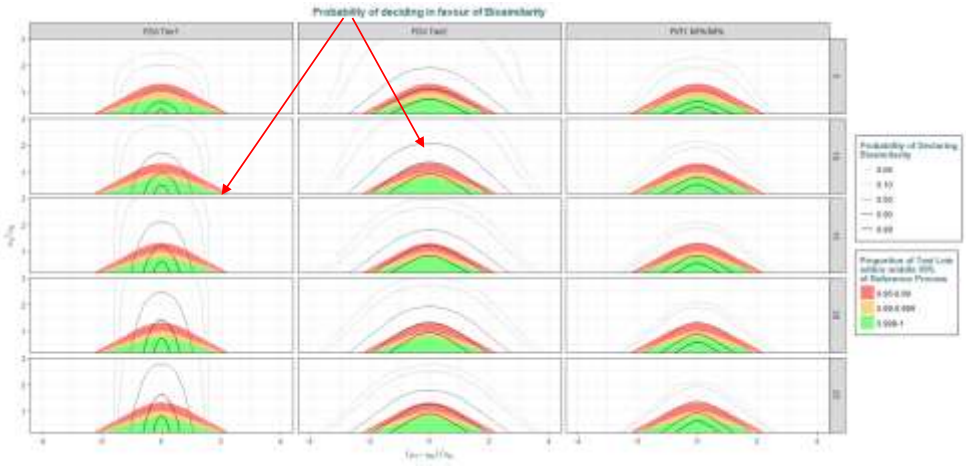
Demonstrate the Operating Characteristics (1)

- Simulate or derive the performance of the decision rule for different combinations of the Mean and SD of the Test Product Process
- E.g.
  - **Assume Reference Mean = 100, Reference SD = 1**
  - **# Reference Lots = 15**
  - **# Test Lots = 5, 10, 15, 20, 25**

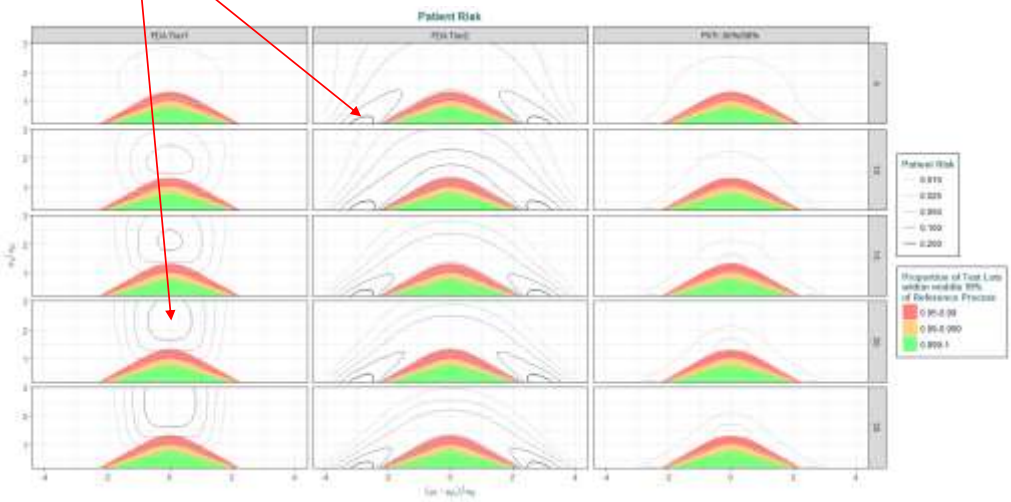
Decision methods:

- FDA Two-Sided 90% Confidence Interval of Mean Difference
- FDA 90% of Test Lots in Mean +/- 3 SD
- Proposal 1 β PI within β/γ TI (80% and 98% chosen here)
- Proposal 2 $Pr(Test\ with\ Limits|Data) \geq 0.90$
- Proposal 3 Pr(Biosimilar | data) ≥ 0.90 (Mike Denham's proposal)

Demonstrate the Operating Characteristics (3)

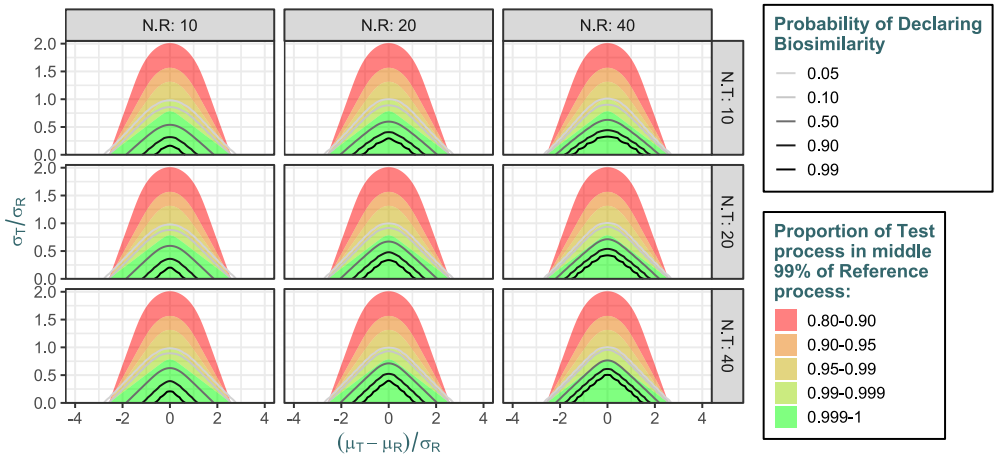


Patient Risk



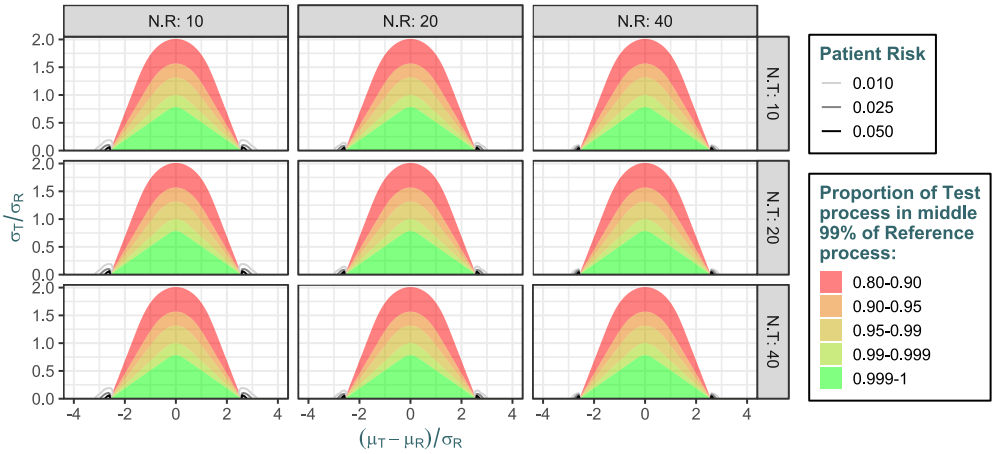
Operating Characteristic based on P(Biosim|Data) > 0.9

Biosimilarity based on $P_T = P_R = 99\%$



Patient Risk[1]

Biosimilarity based on $P_T = P_R = 99\%$ and P(Biosim|Data) > 0.90



ISBS, Kyoto, AUG2019

[1]Declare Test Biosimilar and patient receives Test lot outside middle **99%** of Reference process

Conclusions

- Let's start with a definition of a Biosimilar (or Comparable drug product)
- Compute the probability to decide in favor of the definition (Probability of Success)
- Given the uncertainties of the estimates
- Control patient's risk
- The Bayesian perspective is a natural way to address the question:
  $Pr(Biosimilarity|Data)$ and not $Pr(Data|H0: Not\ Biosimilar)$
- The Bayesian statistics provides the
  - Posterior Predictive Distribution
  - Predictive Probability
  - About future Test batches
- The Operating Characteristics of the Bayesian approach are consistent with the region of Biosimilarity/comparability
- In the future, informative priors could be introduced about
  - Analytical error
  - Reference Drug product

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